

REMARKS/ARGUMENTS

Claims 1-7 and 11-14 are active. The claims have been amended for clarity and consistency with U.S. practice. New Claims 13-14 find support in the paragraph bridging pages 5-6 of the specification. No new matter has been added.

Rejection—35 U.S.C. §112, first paragraph

Claims 10-12 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate enablement. These claims refer to the ability of the proline ester of claim 1 to modulate the activity of an ACE (angiotensin converting enzyme) associated with a pathological condition.

As disclosed on pages 1-4 of the specification the clinical application of ACE inhibitors or angiotensin receptor antagonists are well-known in the art.

One with skill in the pharmaceutical or medical arts would understand that the pro-drug of Claim 1 would be efficiently converted to the active drug enalaprilat during percutaneous absorption and exhibit the known effects of the ACE inhibitor enalaprilat.

Therefore, the Applicants respectfully request that this rejection be withdrawn.

Rejection—35 U.S.C. §112, second paragraph

Claims 8-10 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is moot in view of the amendments above.

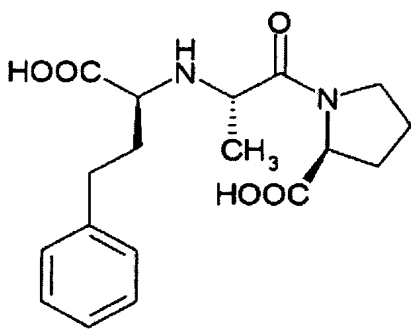
Rejection—35 U.S.C. §101

Claims 8-10 were rejected under 35 U.S.C. 110, as being directed to non-statutory “use” claims. This rejection is moot in view of the amendments above.

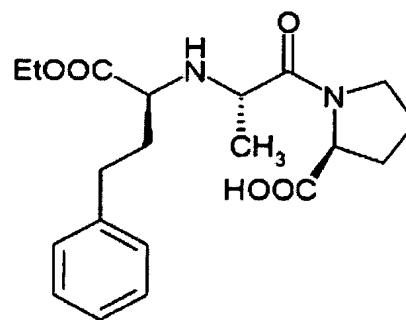
Rejection—35 U.S.C. §103

Claims 1 and 2 were rejected under 35 U.S.C. 103(a) as being unpatentable over Fodor et al., HU 196834, in view of Green et al., Protective Groups in Organic Chemistry, 3<sup>rd</sup> edition, pages 382, 388 and 390. The prior art does not render the compound of independent Claim 1 obvious, because it does not suggest selecting the specific substituents at positions R1 and R of the prior art structure. Namely, the claimed compound requires that R1 be methyl and that R be selected from the group consisting of a hydroxy-lower alkyl group, a lower alkoxy-lower alkyl group, or a lower alkoxy-lower alkoxy-lower alkyl group. On the other hand, in the Fodor compound, R1 may be any alkyl or alkylamino and R may be any protective group. Thus, the prior art discloses an unlimited genus of different compounds, while Claim 1 is directed to a limit subgenus of compounds.

Moreover, one with ordinary skill in the art would understand that small modifications to the core structure of this class of ACE inhibitors have drastic effects on drug activity since the replacement of a single hydroxy group on the active ACE inhibitor enalaprilat converts it into the inactive prodrug enalapril (see structural comparison below).



Enalaprilat (active ACE inhibitor)



Enalapril (pro-drug)

The prior art provides no reasonable expectation of success that the limited subgenus of prodrug compounds covered by Claim 1 would have stability, the ability to be percutaneously absorbed, and the ability to convert to the active drug enalaprilat in the skin.

For example, the generic structure of Fodor reads on enalaprilat (when R1 is methyl and R is hydrogen). Unlike the claimed compounds, enalaprilat lacks stability even if it is somewhat absorbable as disclosed on the bottom paragraph of page 2 of the specification).

On the other hand, the inventors have demonstrated that the inventive compounds have superior percutaneous absorbability and stability, as well as the ability to be converted to the active drug in the skin without the need for conversion in the liver, see Tables 1 and 2 on pages 37-38 of the specification. As shown there, not all prodrugs of enalaprilat have these properties. For example, the comparative example in Tables 1 and 2 show that the prodrug enalapril lacks stability and is not converted to the active ACE inhibitor enalaprilat in the skin.

Table 2 on page 38 of the specification demonstrates that three representative pro-drug compounds of the invention (Inventive compounds 1, 2 and 3) were permeated through the 3 dimensional cultured human skin model and were converted to enalaprilat at an efficiency ranging from about 64-77%. By comparison, only about 1.2% of the drug enalapril (a different pro-drug of enalaprilat, see the comparative example) was converted to enalaprilat. These data show the superiority of the prodrugs of the present invention compared to other enalaprilat prodrugs like enalapril. That is, the prodrugs of the invention are percutaneously absorbed by human skin and are efficiently converted to the active ACE inhibitor enalaprilat without the need for the long period of time required for prodrug circulation to the liver.

The lack of a reasonable expectation of success for the present invention is also illustrated by the data shown in the attached Declaration.

Comparative Compounds 1 and 2 having an unsubstituted alkyl group have good stability and convertibility, but have poor skin permeability (0.73 or 0.93).

Comparative Compounds 3-6 in which both carboxyl groups are substituted also have poor skin permeability and are converted to enalapril, not to enalaprilat.

Comparative Compounds 7-10 have extremely poor stability.

The prior art does not suggest selecting the particular prodrug compounds of independent claim 1, nor does it provide a reasonable expectation of success that this limited subgenus of compounds would have the superior percutaneous absorption, stability, and conversion properties shown in the specification and in the attached Declaration. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

#### Objections—Claims

Claims 2-12 were objected to as depending from a rejected base claim. Claims 2 and 8-12 were previously rejected. However, in view of the amendments and remarks above, the Applicants submit that these claims should now be in condition for allowance.

Claim 6 was objected to as being improperly multiple dependent. This objection is moot in view of the amendment above.

Conclusion

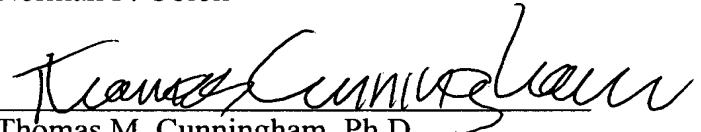
In view of the amendments and remarks above, the Applicants respectfully submit that this application is now in condition for allowance. An early notification to that effect is earnestly solicited.

Respectfully submitted,

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